6. ADDITIONAL WORK UNDERTAKEN BY THE ERG

The ERG identified and corrected the following errors identified during the review:

- In the reporting of outputs, the number of bleeding events was inverted between the two arms ([redacted])
- The lack of uninformative priors being incorporated for the parameters for the Beta distribution in those variables where no events were observed.
- Finally, an error is corrected for the probability of PE recurrences ([redacted]) after the first year (which had been incorrectly divided by 4).

The ERG comment that these amendments made no material difference to the ICER.

Additional work was undertaken by the ERG to explore other plausible scenarios on INR monitoring costs, and assuming that the proportion of VTEs that are PEs might be different between the two arms. It was not possible for the ERG to explore the impact of amending assumptions for other issues identified during the review due to time and resource constraints, and data limitation.

The ERG explored a scenario analysis assuming less intensive INR monitoring for patients treated with a VKA compared with the assumptions used by the manufacturer. After consultation with the clinical advisors to the ERG, the following assumptions have been made;

a. 6 INR monitoring visits the first 3 months and 3 INR visits thereafter (instead of 9 at first and 5 thereafter assumed by the manufacturer)

b. 75% of visits in the primary care are done by nurses (instead of a split 50/50 assumed by the manufacturer)

c. Follow-up visits in secondary care are done by non-consultants led only (instead of assuming a mix of consultants and non-consultants led)

The impact of these assumptions were to result in the cost of INR monitoring of £320 for patients treated with warfarin for 12 months. A lower figure (£241) for this value was used in a recent single technology appraisal of dabigatran,[77] however this was for patients with atrial fibrillation, which is believed by the clinical experts to the ERG to require less intensive monitoring.

A scenario analysis was also conducted to examine the impact on results assuming that the proportion of VTEs that are PEs is treatment-specific, using data from the EINSTEIN-DVT trial. Whilst the difference did not reach statistical significance (p=0.14) this could be due to a small number of events. Given the marked differences in the health and financial consequences following PE or DVT conducting an exploratory analysis was deemed prudent. The analysis assumes that;

a. [redacted] VTEs are DVTs in patients treated with dual therapy LMWH/VKA
b. [redacted] VTEs are DVTs in patients treated with rivaroxaban

Finally, a cost-minimisation was undertaken assuming the treatment effect to be the same between rivaroxaban and LMWH/VKA. This scenario assumes that the two drugs provide the same clinical benefits, but are associated with different costs in terms of drug acquisition, administration and monitoring.

Results are presented using a lifetime horizon for the PSA results only (1,000 iterations) as the model showed non-linearity when comparing the results from the deterministic and probabilistic analysis. In addition to the ICER, the net monetary benefit (NMB) at a WTP of £20,000 or £30,000 per QALY gained was also reported. A positive NMB indicates that rivaroxaban is cost-effective at the examined WTP. Finally, the analyses use data by intended treatment duration.

Note that the interpretation of the probabilistic results is limited due to Bayer's application of methods in the model which are not entirely appropriate.

6.1. Probabilistic cost-effectiveness results in patients for whom 3 months of anticoagulation treatment is appropriate – exploratory analyses conducted by the ERG.

A summary of the analyses undertaken by the ERG are provided in Table 37; care must be taken in interpreting the cost-effectiveness of interventions which are cost saving but provide a reduction in overall QALYs.

Table 37 Summation of ERG exploratory analyses in patients for whom 3 months of anticoagulation treatment is appropriate.

		Incremental Cost (£)	Incremental QALY	Cost Per QALY lost (£) *
1	Manufacturer Basecase	-180	-0.02	11,787
2	As 1, but errors corrected	-182	-0.02	11,792
3	As 2 with INR monitoring costs altered	-86	-0.01	6,358
4	As 2 with differential PE:DVT ratio assumed	-170	-0.03	5,031
5	As 2 with INR monitoring costs altered and with differential PE:DVT ratio assumed	-75	-0.04	2,123
* When evaluating cost per QALY lost, values greater than the assumed threshold are deemed cost-effective, with values under the threshold indicating that a treatment would not be cost-effective				

More detailed results for the different analyses are presented in Table 38 to Table 42 with the mean incremental cost and QALY values plotted in Figure 20.

Figure 20: additional work undertaken by the ERG - cost effectiveness plane in patients for whom 3 months of anticoagulation treatment using other plausible assumptions

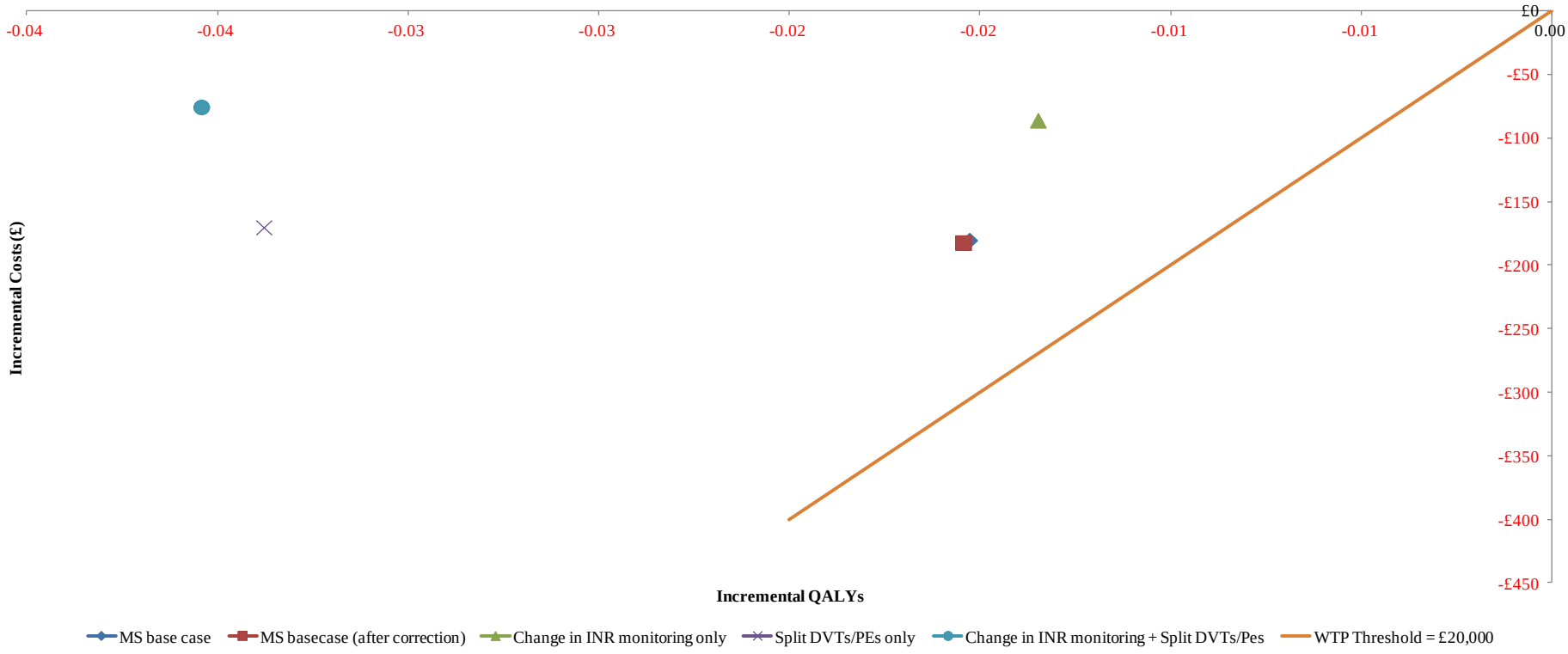

Table 38: Probabilistic base case analysis (in patients treated for 3 months) using the manufacturer's assumptions (before amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	£11,787 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£245	-£245
Event costs	£706	£689	£18
Bleed cost	£81	£160	-£79
PTS/CTEPH	£184	£175	£9
Total Cost	£1,187	£1,367	-£180
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.10	1.08	0.01
No of maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	13.32	13.33	-0.02
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£125.41**	**-£278.12**	

Table 39: Probabilistic base case analysis (in patients treated for 3 months) using the manufacturer's assumptions (after amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	£11,792 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£241	-£241
Event costs	£892	£874	£18
Bleed cost	£80	£165	-£84
PTS/CTEPH	£298	£289	£9
Total Cost	£1,486	£1,668	-£182
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.23	1.22	0.01
No of maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	12.98	13.00	-0.02
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£126.66**	**-£280.97**	

Table 40: Probabilistic base case analysis (in patients treated for 3 months) after amendment of errors identified in the model, assuming less intensive INR monitoring (same split DVTs/PEs between arms).

LIFETIME (40 years)	ICER estimate:	6,358 per QALY yielded	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£139	-£139
Event costs	£730	£714	£16
Bleed cost	£77	£165	-£88
PTS/CTEPH	£293	£285	£8
Total Cost	£1,316	£1,402	-£86
Outcomes			
No of deaths	0.94	0.94	0.00
No VTEs	1.23	1.21	0.01
No maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	12.98	12.99	-0.01
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£183.76**	**-£318.46**	

Table 41: Probabilistic base case analysis (in patients treated for 3 months) using the manufacturer's assumptions on INR monitoring (after amendment of errors identified in the model) and assuming a different split DVTs/PEs between treatment arms.

LIFETIME (40 years)	ICER estimate:	£5,031 per QALY yielded	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£240	-£240
Event costs	£891	£870	£21
Bleed cost	£79	£161	-£81
PTS/CTEPH	£296	£282	£13
Total Cost	£1,482	£1,651	-£170
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.22	1.21	0.01
No of maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	12.96	12.99	-0.03
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£505.59**	**-£843.35**	

Table 42: Probabilistic base case analysis (in patients treated for 3 months) after amendment of errors identified in the model assuming less intensive INR monitoring and assuming a different split DVTs/PEs between treatment arms.

LIFETIME (40 years)	**ICER estimate:**	2,123 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£142	-£142
Event costs	£743	£723	£21
Bleed cost	£75	£160	-£85
PTS/CTEPH	£301	£287	£14
Total Cost	£1,335	£1,410	-£75
Outcomes			
No of deaths	0.94	0.94	0.00
No VTEs	1.23	1.21	0.01
No maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	12.97	13.00	-0.04
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£633.11**	**-£987.26**	

6.2. Probabilistic cost-effectiveness results in patients for whom 6 months of anticoagulation treatment is appropriate – exploratory analyses conducted by the ERG.

A summary of the analyses undertaken by the ERG are provided in Table 43; care must be taken in interpreting the cost-effectiveness of interventions which are cost saving but provide a reduction in overall QALYs.

Table 43. Summation of ERG exploratory analyses in patients for whom 6 months of anticoagulation treatment is appropriate.

		Incremental Cost (£)	**Incremental QALY**	**Cost Per QALY gained or *lost* (£) ***
1	Manufacturer Basecase	-101	0.01	Dominant
2	As 1, but errors corrected	-104	0.01	Dominant
3	As 2 with INR monitoring costs altered	71	0.01	8,341
4	As 2 with differential PE:DVT ratio assumed	-91	-0.00	*26,343*
5	As 2 with INR monitoring costs altered and with differential PE:DVT ratio assumed	84	-0.00	Dominated
* When evaluating cost per QALY lost, values greater than the assumed threshold are deemed cost-effective, with values under the threshold indicating that a treatment would not be cost-effective				

More detailed results for the different analyses are presented in Table 44 to Table 48 with the mean incremental cost and QALY values plotted in Figure 21.

Figure 21: additional work undertaken by the ERG - cost effectiveness plane in patients for whom 6 months of anticoagulation treatment using other plausible assumptions

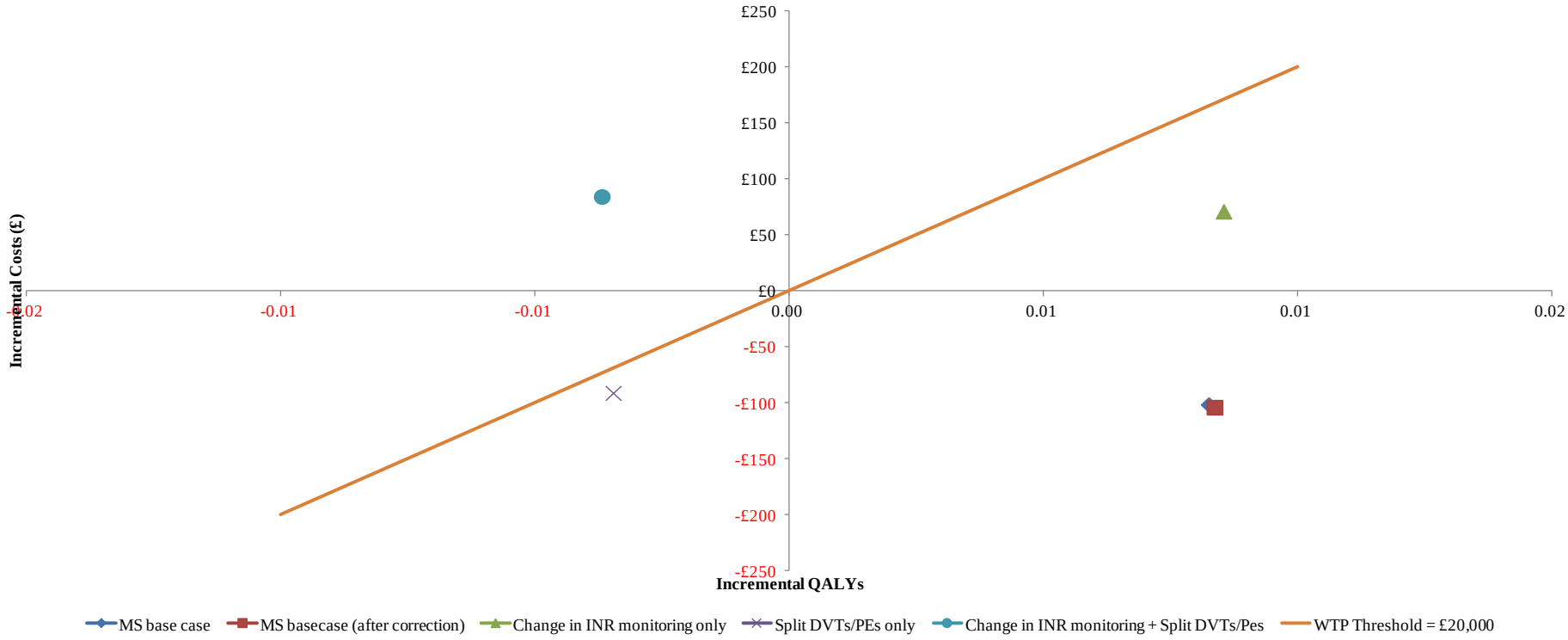

Table 44: Probabilistic base case analysis (in patients treated for 6 months) using the manufacturer's assumptions (before amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£394	£105	£289
Monitor cost	£0	£366	-£366
Event costs	£685	£689	-£4
Bleed cost	£92	£111	-£19
PTS/CTEPH	£174	£176	-£2
Total Cost	£1,345	£1,447	-£101
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.08	1.08	-0.00
No of maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.36	13.35	0.01
	WTP = £20,000	**WTP = £30,000**	
NMB	**£266.58**	**£349.14**	

Table 45: Probabilistic base case analysis (in patients treated for 6 months) using the manufacturer's assumptions (after amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£394	£105	£289
Monitor cost	£0	£370	-£370
Event costs	£865	£869	-£4
Bleed cost	£91	£108	-£17
PTS/CTEPH	£290	£292	-£2
Total Cost	£1,640	£1,744	-£104
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.21	1.21	-0.00
No of maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.02	13.01	0.01
	WTP = £20,000	**WTP = £30,000**	
NMB	**£271.29**	**£355.00**	

Table 46: Probabilistic base case analysis (in patients treated for 6 months) after amendment of errors identified in the model, assuming a less intensive INR monitoring (same split DVTs/PEs between arms).

LIFETIME (40 years)	ICER estimate:	8,341 per QALY gained	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£394	£105	£289
Monitor cost	£0	£197	-£197
Event costs	£721	£724	-£4
Bleed cost	£94	£109	-£15
PTS/CTEPH	£291	£293	-£2
Total Cost	£1,500	£1,428	£71
Outcomes			
No of deaths	0.94	0.94	-0.00
No VTEs	1.21	1.22	-0.00
No maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.01	13.00	0.01
	WTP = £20,000	**WTP = £30,000**	
NMB	**£99.68**	**£185.17**	

Table 47: Probabilistic base case analysis (in patients treated for 6 months) using the manufacturer assumptions about INR monitoring (after amendment of errors identified in the model) and assuming a different DVT/PE split between treatment arms.

LIFETIME (40 years)	ICER estimate:	£26,343 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£394	£105	£289
Monitor cost	£0	£365	-£365
Event costs	£867	£868	-£1
Bleed cost	£96	£113	-£17
PTS/CTEPH	£305	£302	£3
Total Cost	£1,662	£1,753	-£91
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.21	1.22	-0.00
No of maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.01	13.01	-0.00
	WTP = £20,000	**WTP = £30,000**	
NMB	**£21.93**	**-£12.65**	

Table 48: Probabilistic base case analysis (in patients treated for 6 months) after amendment of errors identified in the model, assuming less intensive INR monitoring and assuming a different DVT/PE split between treatment arms.

LIFETIME (40 years)	**ICER estimate:**	dominated	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£394	£105	£289
Monitor cost	£0	£195	-£195
Event costs	£713	£713	-£0
Bleed cost	£95	£108	-£13
PTS/CTEPH	£292	£289	£3
Total Cost	£1,494	£1,410	£84
Outcomes			
No of deaths	0.94	0.94	0.00
No VTEs	1.21	1.21	-0.00
No maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.01	13.02	-0.00
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£158.14**	**-£194.96**	

6.3. Probabilistic cost-effectiveness results in patients for whom 12 months of anticoagulation treatment is appropriate – exploratory analyses conducted by the ERG.

A summary of the analyses undertaken by the ERG are provided in Table 49.

Table 49: Summation of ERG exploratory analyses in patients for whom 12 months of anticoagulation treatment is appropriate.

		Incremental Cost (£)	**Incremental QALY**	**Cost Per QALY gained (£)**
1	Manufacturer Basecase	-13	0.04	Dominant
2	As 1, but errors corrected	-10	0.04	Dominant
3	As 2 with INR monitoring costs altered	307	0.04	8,089
4	As 2 with differential PE:DVT ratio assumed	-3	0.03	Dominant
5	As 2 with INR monitoring costs altered and with differential PE:DVT ratio assumed	309	0.03	12,183

More detailed results for the different analyses are presented in Table 50 to Table 54 with the mean incremental cost and QALY values plotted in Figure 22.

Figure 22: additional work undertaken by the ERG - cost effectiveness plane in patients for whom 12 months of anticoagulation treatment using other plausible assumptions

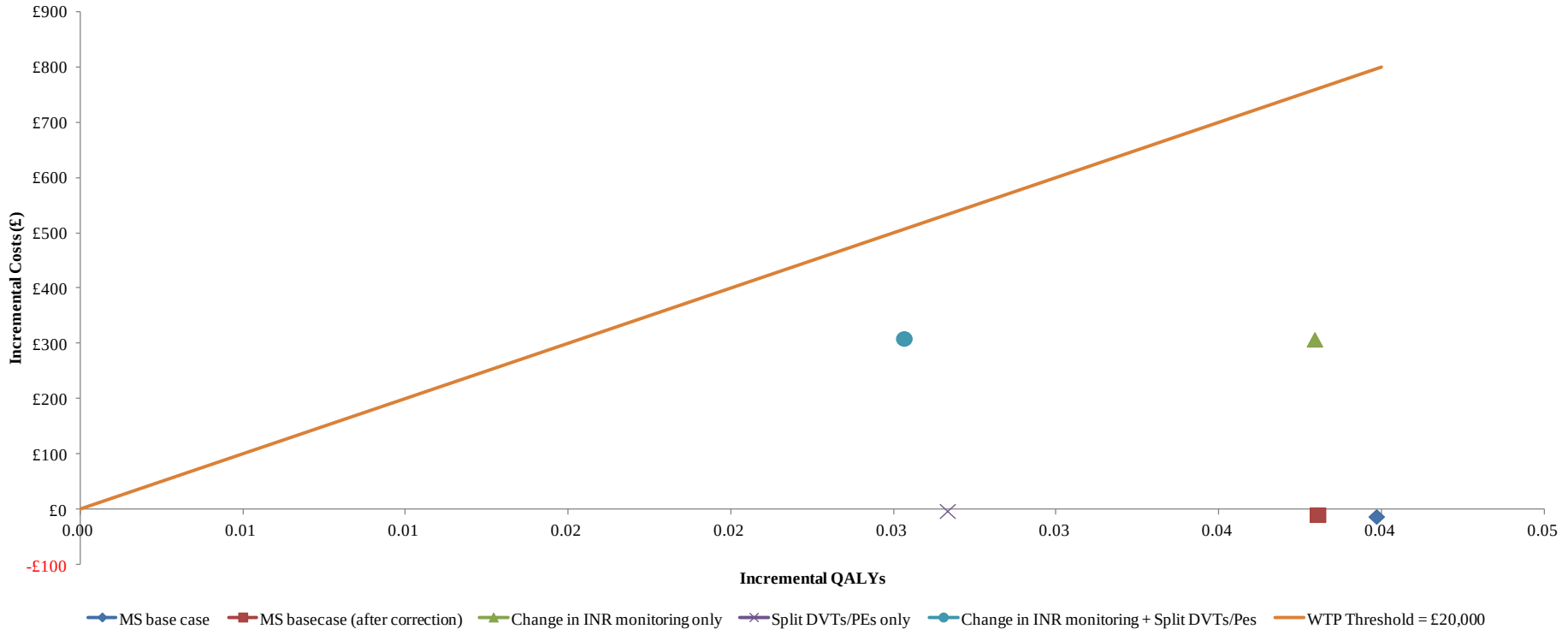

Table 50: Probabilistic base case analysis (in patients treated for 12 months) using the manufacturer's assumptions (before amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£746	£116	£630
Monitor cost	£0	£595	-£595
Event costs	£645	£685	-£39
Bleed cost	£54	£44	£10
PTS/CTEPH	£163	£183	-£19
Total Cost	£1,608	£1,621	-£13
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.05	1.08	-0.03
No of maj Bleeds	0.00	0.00	0.00
QALYs (discounted)	13.39	13.35	0.04
	WTP = £20,000	**WTP = £30,000**	
NMB	**£810.27**	**£1,208.75**	

Table 51: Probabilistic base case analysis (in patients treated for 12 months) using the manufacturer's assumptions (after amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£745	£116	£629
Monitor cost	£0	£593	-£593
Event costs	£832	£871	-£39
Bleed cost	£56	£44	£12
PTS/CTEPH	£283	£303	-£20
Total Cost	£1,916	£1,926	-£10
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.18	1.21	-0.03
No of maj Bleeds	0.01	0.00	0.00
QALYs (discounted)	13.06	13.02	0.04
	WTP = £20,000	**WTP = £30,000**	
NMB	**£770.85**	**£1,151.27**	

Table 52: Probabilistic base case analysis (in patients treated for 12 months) after amendment of errors identified in the model, assuming less intensive INR monitoring (same split DVTs/PEs between arms).

LIFETIME (40 years)	ICER estimate:	8,089 per QALY gained	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£745	£116	£629
Monitor cost	£0	£297	-£297
Event costs	£682	£716	-£34
Bleed cost	£66	£37	£28
PTS/CTEPH	£287	£307	-£20
Total Cost	£1,780	£1,473	£307
Outcomes			
No of deaths	0.94	0.94	-0.00
No VTEs	1.18	1.21	-0.03
No maj Bleeds	0.01	0.00	0.00
QALYs (discounted)	13.05	13.02	0.04
	WTP = £20,000	**WTP = £30,000**	
NMB	**£452.00**	**£831.49**	

Table 53: Probabilistic base case analysis (in patients treated for 12 months) using the manufacturer's assumptions about INR monitoring (after amendment of errors identified in the model) and assuming a different DVT/PE split between treatment arms.

LIFETIME (40 years)	ICER estimate:	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£745	£116	£629
Monitor cost	£0	£594	-£594
Event costs	£836	£871	-£35
Bleed cost	£53	£43	£10
PTS/CTEPH	£282	£296	-£14
Total Cost	£1,916	£1,920	-£3
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.18	1.21	-0.03
No of maj Bleeds	0.00	0.00	0.00
QALYs (discounted)	13.05	13.03	0.03
	WTP = £20,000	**WTP = £30,000**	
NMB	**£536.49**	**£803.10**	

Table 54: Probabilistic base case analysis (in patients treated for 12 months) after amendment of errors identified in the model assuming less intensive INR monitoring and assuming a different DVT/PE split between treatment arms.

LIFETIME (40 years)	ICER estimate:	12,183 per QALY gained	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£745	£116	£629
Monitor cost	£0	£303	-£303
Event costs	£688	£718	-£30
Bleed cost	£63	£36	£27
PTS/CTEPH	£277	£290	-£14
Total Cost	£1,773	£1,464	£309
Outcomes			
No of deaths	0.94	0.94	-0.00
No VTEs	1.19	1.21	-0.03
No maj Bleeds	0.01	0.00	0.00
QALYs (discounted)	13.06	13.03	0.03
	WTP = £20,000	**WTP = £30,000**	
NMB	**£197.97**	**£451.22**	

6.4 Cost-minimisation analysis, assuming the same treatment effect between rivaroxaban and LMWH/VKA

Finally, an analysis was conducted which assumed the same efficacy between the two drugs. This analysis, therefore, only compares the drug and monitoring costs.

Using the manufacturer assumption on INR monitoring, rivaroxaban was cost-saving in patients treated for 3 months (£135) and 6 months (£85), but not in patients treated for 12 months (£16).

Table 55: Drug and monitoring costs by intended treatment duration and treatment arm (using MS assumption's on monitoring)

	Rivaroxaban	LMWH/VKA	Incremental
3 months	£236	£371	-£135
6 months	£427	£512	-£85
12 months	£811	£795	£16

Amending the assumption on INR monitoring, rivaroxaban was associated with an increase in cost in patients treated for 6 months (£123) and 12 months (£382) but not in patients treated for 3 months (saving of £6).

Table 56: Drug and monitoring costs by intended treatment duration and treatment arm (using a less intensive monitoring than assumed by the manufacturer)

	Rivaroxaban	LMWH/VKA	Incremental
3 months	£236	£242	-£6
6 months	£427	£304	£123
12 months	£811	£429	£382

- *Monitoring*

[redacted]. Clarification from the manufacturer was requested as to whether patients treated with rivaroxaban would need to be monitored for liver function in clinical practice. The manufacturer confirmed that no monitoring is required, referring to the draft SmPC stating that no liver or other monitoring is necessary or appropriate.[17] Clinical opinion was also sought and believed these assumptions to be reasonable.

For patients treated with a VKA, the manufacturer assumed that patients received 9 INR visits in the first 3 months of treatment, followed by 5 visits every 3 months thereafter based on data from an observational retrospective study conducted in 119 patients monitored in a secondary care anticoagulation service.[27] There are concerns as the data are taken from a single centre and in patients monitored in secondary care only. Clinical opinion was sought, and different views were expressed. One of our experts found the assumptions used by the manufacturer plausible. Our second clinical expert disagreed with the assumptions made by the manufacturer, and believed that six visits in the first 3 months and 2-3 thereafter would be a more accurate estimate.

The manufacturer further assumed that 66% of INR monitoring visits happen in the primary care and 34% in the secondary care based on a national survey (semi-structure interviews) conducted in healthcare professionals leading anticoagulation care, or PCT/health board recommended knowledgeable persons.[58] This encompassed a total of 78 PCTs in England, three local health boards in Wales and one PCT from a health board in Scotland.

For visits happening in primary care, the manufacturer assumed that half of the visits were undertaken by GPs and the remaining by nurses.[1] Both our experts disagreed with this distribution, suggesting this might be plausible for the first visit, but for follow-up visits, nurses would be more involved and would be responsible for seeing the patient, taking the blood and communicating subsequent dosing and recall instructions, whereas the doctor will only be involved in the dosing on the first visit, unless complications such as bleeding or bruising occurred and GP advice was necessary. Clinical advisors to the ERG suggested that a 25/75% split would be a more accurate estimate. Furthermore, our advisors suggested that there might be costs associated with transportation or phlebotomy service for patients that cannot be transported to the clinic. Such costs would not occur in the rivaroxaban arm.

Summary of uncertainties	Has the impact on the ICER been examined?	If so, what are the results? If not, is it possible to give any indication of the direction of the results?
Are the costs and utility used in the economic model appropriate? Several assumptions have been made by the manufacturer. Is it likely to change the conclusion?	This has been formally examined by the manufacturer in SA	Results were not sensitive to a change in costs and utilities in univariate sensitivity analysis. It is unclear whether conclusions of the cost-effectiveness analysis would change if parameters were varied simultaneously. However, this is considered in the PSA.

To further explore this issue, the ERG also sought clarification from the manufacturer on the levels of monitoring observed in the EINSTEIN-DVT trial.[50] The manufacturer stated that the INR monitoring was protocol driven and is therefore not necessarily generalisable to clinical practice in England and Wales. Despite this limitation, data from the trial suggested a mean number of visits of 8.1 for the first 3 months and 4.2 the subsequent quarters. The manufacturer conducted a scenario using the values from the trial and showed that the conclusion remained unchanged.[17]

The ERG acknowledges that the monitoring in the clinical trial[50] was protocol driven but highlight that monitoring in clinical trials is also usually more extensive than in clinical practice and therefore the levels recorded in the trial may suggest that less monitoring visits may occur in real life than are assumed by the manufacturer in the economic model.

Because monitoring is likely to be an important parameter within the calculation of the ICER, the ERG examined further the assumptions on monitoring in the economic model using estimates/advice made by our clinical advisors, i.e.:

- six visits the first three months and 3 visits thereafter (instead of nine visits at first, and five thereafter)
- 25% of visits in the primary care with a GP and the remaining 75% with a nurse (instead of 50/50% split)
- Cost of follow up for non-consultant led visit in secondary care (£18 instead of £24)

Results of this analysis are presented in section 6 of the ERG report. Costs associated with transportation and visit to a phlebotomy service were not included in the absence of robust data about these proportions.

Using the manufacturer's assumptions[1] on the number of visits (nine visits the first three months and five thereafter) and estimated weighted cost per visit (£33.77 for the first INR visit and £26.23 for the subsequent visits), the annual cost of monitoring alone was estimated to be around £656. Using the ERG assumptions, the annual monitoring cost was estimated to be £320 (both values exclude drug acquisition costs but includes some transportation cost). Overall, our estimates of monitoring costs were higher than the figure mentioned by the Northumberland Primary Care Trust (PCT) (about £200/year) or used in the NICE CG92 (£147), but lower than the figure used by the MS (£656).

5.2.3 Comment on validity of results presented with reference to methodology used

In all the analyses conducted by the manufacturer, rivaroxaban was reported to be dominant i.e. led to a saving in costs, but also a gain in QALYs. Savings in costs were however small ranging from £38 to £218 (for the analyses using data by intended treatment duration). The gains in QALYs were similarly small, ranging from 0.0015 to 0.0458 compared with LMWH/VKA.

The ERG noted that the model is non-linear, and that rivaroxaban was not dominant in the PSA in patients treated for 3 months, but provided less QALYs at lower cost. The ICER of rivaroxaban compared with LMWH was £11,792 per QALY yielded in patients treated for 3 months. This has not been reported by the manufacturer. Rivaroxaban remained dominant (providing more QALYs at a lower cost) compared with LMWH/VKA in the PSA in patients treated for 6 and 12 months.

The ERG also noted that the model is based on a series of assumptions, but that there are uncertainties around some of the assumptions made which may impact the ICER due to the very small estimated gain in QALYs and saving in costs with the use of rivaroxaban compared with LMWH/VKA.

The ERG believes that results presented by the manufacturer may be plausible, but there are large uncertainties in the data and the assumptions that were made. The manufacturer estimated the INR monitoring cost to be around £656 annually for patients treated with a VKA. The ERG estimate was around £320 using inputs from our clinical advisors. Similarly, in their submission to this appraisal, the Northumberland PCT reported a value of £200 based on work done in AF. It is unclear what the "true" INR monitoring costs are for patients treated for VTE with a VKA.

There were disagreements within the ERG about the plausibility of assuming that the ratio of DVTs to PEs was independent of treatment received. The ERG sought clinical advice on this matter, and no plausible biological mechanism for a differential effect on DVTs and PEs was offered. [redacted]

The ERG also noted that other assumptions may impact the ICER such as whether the proportion of major bleeds that are IC bleeds are the same between treatment arms, or the assumptions made that the effectiveness is the same by treatment arm once treatment cease.

Finally, the manufacturer did not present an analysis for patients treated beyond 12 months, and only considered the use of rivaroxaban for the treatment of the index event; it is unclear why rivaroxaban was not considered for the treatment of the subsequent recurrences.

The ERG notes that whilst these guidelines point to uncertainty about the benefits of long term treatment, they do not recommend that treatment should cease at 12 months, or give any other suggestions for a maximum treatment duration. In the absence of guidelines recommending against ongoing treatment, and with clinical advice to the ERG indicating that treatment is long term in patients with certain risk factors, amounting to approximately 20% of the DVT population (Personal Communication from Dr Patel and Dr Hampton, December 2011), the ERG remains of the opinion that treatment beyond 12 months in some patients is current practice in England and Wales. Whether this will change in light of the new guidelines is unclear, as the guidelines are not specific on this point. Furthermore, whether clinicians would use rivaroxaban in the same way as current anticoagulant treatment is also unclear, given the lack of evidence beyond 12 months, as stated in the Summary of Product Characteristics (SmPCs)[19,20] which recommend

"The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with Xarelto in this indication for more than 12 months is limited."

Additionally, the manufacturer's EINSTEIN-Ext trial includes patients who are being treated for between 12 months and 2 years. This trial design demonstrates that the manufacturer is aware of ongoing treatment occurring in a proportion of patients in at least some countries. Whilst this does not necessarily indicate that treatment beyond 12 months is common in the UK, it does indicate that international practice includes such long term treatment. The ERG has no reason to believe that UK practice differs significantly from international practice in this, and the manufacturer has not provided any convincing evidence to show otherwise.

Given that there is considerable uncertainty on this point, it would have been prudent for analyses assuming treatment >12 months to have been undertaken by the manufacturer.

A further unrelated point is that, on Page 21 of the MS, the manufacturer states "rivaroxaban will be initiated during a secondary care outpatient consultation". The ERG feel that there will be some variation in this and that in some cases, rivaroxaban would be initiated during inpatient care.

contraindications for the drug (as listed in the SmPC)[19,20], and would therefore appear eligible for treatment, are not included in the trial evidence. These include:

- Additional indications for a vitamin K antagonist
- Creatinine clearance <30 mL/min (but not less <15mL/min)
- Clinically significant liver disease (e.g. acute hepatitis, chronic active hepatitis or cirrhosis) or alanine aminotransferase >3x upper limit of normal (ULN)
- Bacterial endocarditis
- high risk of bleeding
- Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg

Of particular note is the exclusion of patients with high risk of bleeding. This group is specifically mentioned in the NICE scope as a potential subgroup analysis. Whilst it could be argued that these groups required additional resources to treat or different treatment regimes and would therefore have presented practical challenges within the trial, this does not alter the fact that there is no evidence about the action of rivaroxaban in these groups. The manufacturer does not report having sought clinical opinion to explore this.

3.1.1.2 Excluded on basis of index event

According to Table 10, section 5.3.3 of the MS, patients with proximal DVT were not included in the trial." This focus on patients with proximal DVTs would appear to be in line with the expectations of the clinical advisors to the ERG, who felt that this appraisal should focus on proximal DVT patients. However, this distinction is not stated in the NICE scope,[3] nor in the SmPC,[19,20] and the ERG remains unclear on this point.

As evidence is not available for the subgroup discussed above, it is unclear whether the available evidence from different populations is applicable to these subgroups.

The ERG attempted to clarify the distribution of severity of disease within the trial with the manufacturer by asking for the proportion of patients with distal, provoked and spontaneous DVTs The question was not interpreted by the manufacturer as the ERG had intended (the question was intended to related to baseline proportions, but was answered with outcome proportions).[17]

[redacted]

3.1.2 EINSTEIN-Ext Population

3.1.2.1 Inclusion on basis of index event

The EINSTEIN-Ext trial recruited patients with either a DVT or a PE. Whilst these events are thought to be manifestations of the same underlying condition, the inclusion of patients with PE is outside the scope produced by NICE[3] and is also outside the indication described in the marketing authorisation.[1] The ERG requested an analysis of the study results including only DVT patients. This has been fulfilled in part by the manufacturer, though they have decided not to provide analyses of subgroups within the DVT population as the study was not designed with that level of interrogation in mind.[17]

3.1.2.2 Inclusion of those in clinical equipoise

An additional limitation of this study in the context of this assessment is that it only included patients who were in clinical equipoise (in other words patients for whom it was unclear whether continued treatment would be of benefit) and compared treatment with rivaroxaban in this group to treatment with placebo treatment. This choice of comparator is appropriate where it is unclear whether ongoing treatment is beneficial or not. The clinical advisors to the ERG estimate approximately 20% of patients require ongoing anticoagulation (Personal Communication from Dr Patel and Dr Hampton, December 2011). However, the manufacturer's understanding is that this group do not exist in any great numbers.[1,17] It therefore seems unclear how the 20% identified by our clinicians as being in need of ongoing treatment would have been classified for the purpose of this study, and whether they are included or not. It would appear from the protocol (page 5)[22] and the MS (page 40)[1] that this group were identified and excluded, though no definition of how these patients were classified is given.[22] In addition, the manufacturer states that patients who either did or did not require ongoing treatment were excluded (page 37),[1] though the protocol does not mention the exclusion of patients who do not need treatment explicitly. The ERG feels, therefore, that the population in the EINSTEIN-Ext trial is not adequately defined.

3.1.2.3 Exclusion on basis of comorbidities or patient characteristics

EINSTEIN-Ext also had very similar exclusion criteria to EINSTEIN-DVT and is therefore subject to the same criticisms as outlined in section 3.1.1.1

3.4.2 Outcomes recommended by EMA research guidelines[23]

Whilst all the outcomes specified by NICE were reported (with the exception of HRQoL), some of the outcomes specified in the EMA document were not reported. The EMA guidelines recommend a composite primary outcome of "recurrent, symptomatic, nonfatal DVT/PE and mortality," with the two additional analyses; the combined incidence of recurrent DVT/PE and VTE-related deaths, with secondary analyses for each individual component separately (priority for non-inferiority trials) and the combined incidence of recurrent DVT/PE and all deaths, with secondary analyses for each individual component separately (priority for Superiority trials).

The EMA primary outcomes were not reported in the corresponding EINSTEIN trials. However, all the individual components of these composite primary outcomes were reported, and it is stated in the EPAR (published after production of this report) that the EMA were satisfied with the outcomes. These outcomes were not specified in the NICE scope, and the ERG does not feel that their omission is problematic; composite outcomes are generally not used in economic analyses as there are differential impacts on both costs and utility for the constituent events, and whilst composite outcomes may seem to have simplicity on their side, they can be criticised for obscuring important differences in outcomes.[29]

3.4.3 Composite primary endpoint

This last point is of further interest as the primary outcome defined by NICE is itself a composite outcome. VTE recurrence includes both DVT and PE. PEs are generally caused by parts of a DVT clot breaking off and getting lodged in the arteries of the lungs. Whilst these two events are manifestations of the same underlying condition, the clinical implications of each are different, with PE being more associated with death and CTEPH. There are also different costs associated with each. The use of a composite outcome might be argued to be valid if the constituent events are not thought to differ in their response to treatment, i.e. they have similar reductions in relative risk.[29] If there is reason to believe that the two events may behave differently, then the composite outcome may not be appropriate.

3.4.4 The diagnosis of primary outcomes

The diagnosis of DVT and PE, for both index events and recurrence, described in the MS are largely consistent with those recommended by the European Medicines Agency (EMA) Committee for Proprietary Medical Products (CPMP)[23] guidelines for the evaluation of new technologies for managing VTE. Exceptions are discussed later in the report in section 4.2.1.3, "*difference between expected and confirmed events*".

4.1.4.1 Concealment of treatment allocation

The question "was the concealment of treatment allocation adequate" was answered as "N/A" by the manufacturer. This may be because the trial is open label. However, this question relates to the concealment of allocation up to the point of randomisation, where the important factor is whether study personnel can predict which group a patient will be allocated to before allocation takes place. This can result in selection bias. It is the opinion of the ERG that this should have been attempted, and that a NA answer is not appropriate. However, the trial arms [redacted] so it is unlikely that selection bias has affected the results.

[redacted]

The ERG agrees, given the manufacturer's response, that the scoring is acceptable.

4.1.4.3 Blinding of outcome assessors

In addition, in light of responses received by the ERG,[17] the ERG have some concerns relating to the blinding of outcome assessors. This is discussed elsewhere in the report (section 4.2.1.3, "Difference between suspected and confirmed events").

- However, the study design did not include a power calculation for each of the intended treatment duration groups. As a result, it is unclear whether the subgroups are powered to detect an effect, and the ability to draw conclusions as to the relative efficacy in each treatment duration subgroup is limited.

- The primary study outcomes were defined in line with the NICE scope,[3] and were similar to the outcomes recommended by the EMA.[23] However, neither of these documents specified whether data should be collected as time to event data, or simply as frequency data. Time to event data really only provides information about whether the time to the first event is lengthened. However, as DVTs can recur multiple times in an individual patient within the timeframe of these trials, and each recurrence carries with it its own costs and QALY implications, it is unclear if the time to the first event is reliably linked to overall frequency, and whether this type of data is adequate to populate a long term model where multiple recurrences can occur. As patients were censored once they had had a VTE event, frequency data was not reported for this trial.

- The EINSTEIN-DVT trial is a non-inferiority trial. This is appropriate as it would have been unethical to conduct a placebo-controlled trial, given that there are treatments already available that are potentially lifesaving and preventative of irreversible damage.[38] Draft US Food and Drug Administration (FDA) guidelines recommend that where non-inferiority trials are conducted and a placebo arm cannot be included due to ethical considerations, some other evidence should be submitted to show that the effects seen in the non-inferiority trial are equivalent to previous measures of efficacy for the comparator drug. This is known as showing that the trial has assay sensitivity:

  > "If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug." (Page 3)

  No evidence of assay sensitivity was provided, so it is unclear whether the effects seen in EINSTEIN-DVT were representative of other estimates of the efficacy of Enoxaparin/VKA treatment. This could work in favour of or against rivaroxaban, as the estimate of efficacy for Enoxaparin/VKA in EINSTEIN-DVT could theoretically be either an overestimate or an underestimate.

However, the ERG additionally believes that because of the way the (network) meta-analysis has been implemented, the results of this analysis may not provide a good estimate of the uncertainty associated with the true treatment effect, although the point estimate may be reasonable. See below for more discussion on this point. The point estimate shows rivaroxaban to be less effective than LMWH for VTE (HR 1.32 (95% Credible Interval (CrI), 0.06 to 32.3), whilst major bleeding is better (OR 0.24 (95% CrI, 0.00 to 9.44) and non-major bleeding is worse (OR 1.61 (95% CrI, 0.11 to 26.5). Considering the results across the three analyses, it would appear however, that a choice of the primary analysis would have disadvantaged rivaroxaban. The ERG remains unconvinced about the appropriateness of the analyses as they have been implemented.

- Tau values – in meta-analyses the parameter Tau is commonly used to describe the between-study standard deviation. The MS presents tables of results including estimates of precision (i.e. the inverse of the variance), which are labelled as tau. The ERG believes that estimates of the between-study standard deviation would be more informative.

- It is argued that only dalteparin is licensed specifically in people with cancer in the UK. However, enoxaparin and tinzaparin do not appear to be contraindicated in those with cancer, so the rationale for only looking at data from Lee 2003[43] seems weak (page 73, 78).

In addition, the ERG has a number of technical issues with the conduct of the MTC, as outlined here.

4.4.1 MTC methods in relation to NICE DSU TSD2

Section 5.7.5 of the submission presents the results of random effects (network) meta-analyses of hazard ratios for VTE recurrence, and of binary data for VTE recurrence, clinically relevant non-major bleeding and major bleeding.

The analysis was conducted following the general guidance outlined in NICE DSU TSD2.[47]
Treatment effects are estimated using Markov chain Monte Carlo methods. These combine sample data with external information which is characterised using prior distributions for the parameters in the model. Ideally the analysis would incorporate genuine prior information, although when there is sufficient sample data this tends to dominate any prior information that may be available so that eliciting it from experts is often not efficient. In most practical examples, such as this STA, it is common to incorporate prior information using reference prior distributions. Such prior distributions are often thought of as being non-informative, although whether they are truly non-informative

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

Whilst much of the systematic review was conducted well, and the report itself was well presented, there were minor issues with the conduct and reporting of the systematic review, including:

- Poorly defined inclusion and exclusion criteria
- Study selection process lacked transparency
- Data extraction strategy was not well documented
- Quality assessment scoring was queried in three cases by the ERG, and some doubt around the answers and potential for bias remains.

However, the review was thought to be largely reliable by the ERG, and the included trials were of good quality, regardless of these issues.

Data from two trials were presented. Data from the EINSTEIN-DVT trial was considered the most relevant to this appraisal. In this multi-centre, phase III, non-inferiority randomised controlled trial (RCT), rivaroxaban appeared non-inferior to treatment with enoxaparin/VKA for safety and efficacy outcomes. The overall hazard ratio (HR) was 0.68 (95% confidence interval (CI), 0.44 to 1.04) for the primary efficacy outcome VTE recurrence, and for the primary safety outcome of clinically relevant bleeding, the HR is 0.97, (95% CI 0.76-1.22). All cause mortality HR was 0.67 (0.44 to 1.02). Rivaroxaban also appeared non-inferior in terms of adverse events and mortality.

[redacted] The interaction test was significant when interpreted at the [redacted], and the treatment would appear to not have been proven to be equivalent in the 3 month intended treatment duration group. Bleeding events across these groups, however, looked largely similar.

Data from the EINSTEIN-Ext trial was also presented. This multi-centre, phase III RCT compared rivaroxaban to placebo in a group of patients with an index event of DVT or PE who had completed 6 or 12 months of treatment, and where it was unclear whether ongoing treatment would be advantageous or not (i.e. patients were in "clinical equipoise). Rivaroxaban was shown to be statistically superior to placebo for prevention of VTE recurrence, with an HR of 0.18 (95% CI, 0.09 to 0.39), though its safety profile was statistically significantly worse, with an HR of 5.19 (95% CI, 2.3 to 11.7) for the outcome of clinically relevant bleeding. [redacted]

Table 4: Rivaroxaban characteristics. Compiled by the ERG using information given on pages 11 to 13, and in Table 2, page 15 of MS.[1]

Brand name	**Xarelto**
Approved name	**Rivaroxaban**
Therapeutic class	**Oral anticoagulant**
Anticipated indication (confirmed in December 2011)[19,20]	Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE), follow an acute DVT in adults.
Mode of action	Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.
Pharmaceutical formulation	15 mg and 20 mg film-coated tablets are relevant to this appraisal
Acquisition cost (excluding VAT)	The indicative price is £2.10 per tablet. The acquisition cost may be further enhanced by local rebate agreements between the manufacturer and appropriate NHS budgetholders (as per PPRS 2009, paragraph 6.45[24])
Method of administration	Oral
Doses	15 mg and 20 mg
Dosing frequency	15 mg twice daily for 21 days, then 20 mg once daily[19,20]
Average length of a course of treatment	3-12 months according to assessment of individual risk-benefits, according to the MS[1].*
Average cost of a course of treatment	The cost would be £235.86, £427.61 and £811.13 for 3, 6 and 12 months of treatment respectively
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	The SmPC advises a reduced dose in patients with moderate or severe renal impairment (i.e. creatinine clearance < 50 ml/min). The reduced dose would be 15 mg twice daily for 21 days, then 15 mg once daily.[19,20]
* The ERG disagrees with the manufacturer's understanding of length of treatment, and do not know how the assumptions made by the manufacturer on this point will affect average length of a course of treatment.	

Marketing authorisation was gained for rivaroxaban during the course of this assessment and the SmPCs have been published.[19,20]

4.2.1.3 Results and interpretation – EINSTEIN-DVT

Table 10 summarises the key outcome data reported in the MS for EINSTEIN-DVT.

Efficacy outcomes – EINSTEIN-DVT

In the EINSTEIN-DVT trial, the manufacturer states that

"rivaroxaban would be considered statistically significantly non-inferior to comparator therapy if the upper limit of the two sided 95% confidence interval (CI) for the (HR) ratio was below the pre-defined non-inferiority margin of 2.0. This margin corresponds to maintenance of at least 50% of the proven efficacy of standard therapy and was derived based on a comprehensive meta-analysis of historical trials in this indication" (MS, page 47 to 48).[1]

EINSTEIN-DVT reports an overall hazard ratio of 0.68 (95% CI, 0.44 to 1.04) for the primary efficacy outcome, VTE recurrence, when compared to Enoxaparin/VKA, which suggests rivaroxaban is non-inferior to the comparator ($p<0.001$). A test for superiority did not prove significant ($p=0.0764$). The components (PE and DVT) of this composite outcome are listed in Table 10. DVT events appear to have occurred less often in the rivaroxaban arm, whilst PE events appear to have occurred approximately equally in each arm. For the primary safety outcome of clinically relevant bleeding, the HR is 0.97, (95% CI 0.76-1.22, $p=0.77$), which suggests rivaroxaban is non-inferior to the comparator. All cause mortality was 0.67 (95% CI 0.44 to 1.02, $p=0.06$), again indicating non-inferiority. [redacted]

Table 10: Summary of outcomes for EINSTEIN-DVT, taken from table 18 and 29, data on page 56, 58, 65, 96 of MS[1] and Bauersachs et al. 2011[21]

Trial name	**Einstein-DVT**		
References	Bauersachs et al 2010 [21] Manufacturer's submission		
Group	**Rivaroxaban N, (%)**	**LMWH/Enoxaparin N, (%)**	**Hazard ratio (95% CI, p value)**
ITT population: Safety population: PP population:	1731 1718 1525	1718 1711 1571	NA
Primary outcome VTE recurrence			
ITT population: PP population:	36 (2.1) NR	51 (3.0) NR	0.68 (0.44 to 1.04, p<0.001) [redacted]
Secondary outcomes (ITT population)			
Fatal PE	1 (0.1)	0 (0)	NR
PE cannot be ruled out	3 (0.2)	6 (0.3)	NR
Nonfatal PE	20 (1.2)	18 (1.0)	NR
Recurrent DVT plus PE	1 (0.1)	0 (0)	NR
Recurrent DVT	14 (0.8)	28 (1.6)	NR
(safety population)			
Clinically relevant bleeding	139 (8.1)	138 (8.1)	0.97 (0.76 to 1.22, p=0.77)
Major bleeding	14 (0.8)	20 (1.2)	0.65 (0.33 to 1.30, p=0.21)
Clinically relevant non-major bleeding	126 (7.3)	119 (7.0)	NR
Vascular events On treatment Off treatment (30 day follow-up)	 12 (0.7) 1 (<0.01)	 14 (0.8) 4 (0.2)	0.79 (0.36 to 1.71, p=0.55)
All cause mortality	38 (2.2)	49 (2.9)	0.67 (0.44 to 1.02, p=0.06)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Any treatment emergent AE	1078 (62.7)	1080 (63.1)	NR
[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	201 (12.0)	233 (13.6)	NR
Serious, drug related AE	[redacted]	[redacted]	[redacted]
Cause of Death			
PE or PE not ruled out	4 (0.2)	6 (0.3)	NR
Bleeding	2 (0.1)	5 (0.3)	NR

It remains unclear why these patients were included, and whether their inclusion affects the results. In addition, these patients were not routinely excluded from the PP analysis, (though two were excluded, presumably for other reasons, according to the Manufacturer's clarifications (Personal Communication from Bayer plc, December 2011)), even though their clearance levels could be interpreted as a major deviation from the study protocol, and should therefore have been excluded.

- **Patient with PE index event.** These patients were excluded in the PP analysis. A comparison of the ITT analysis with the PP analysis indicates that the estimate of efficacy is not altered, although this analysis involved the exclusion of patients additional to those with index PE. The ERG feels it is unlikely that the inclusion of patients with PE has introduced bias.
    - HR of 0.68 (95% CI 0.44 to 1.04) in the ITT population

[redacted]

Analysis by compliance level. The ERG asked the manufacturer to offer potential explanations for the apparent differences in efficacy in the treatment duration subgroups. Based on clinical advice, the ERG was especially interested in exploring the possibility that compliance in the comparator arm or the rivaroxaban arm may have driven the apparent difference in efficacy. The manufacturer provided the following explanation, which goes some way to exploring the relationship between time in target range and efficacy, which could be considered a product of compliance (at least in part), but does not address issues of compliance directly:

[redacted]

In addition, compliance data is provided elsewhere in the manufacturer's response to the ERG request for clarifications[17] (reproduced here as Figure 5), and whilst no formal analysis has been completed,

- There is some doubt about the appropriateness of the use of a composite outcome (see section 3.4).

The ERG has an additional comment:

- From the analyses provided in the trial it is not possible to tell which patients had 12 months treatment in total, and which had more than 12 months in total. Some may have received up to 2 years treatment. Whilst the manufacturer states that the proportional hazard assumption held, [redacted] these results were not presented as subgroup analyses.

4.2.2.3 Results and interpretation – EINSTEIN-Ext

Efficacy outcomes – *EINSTEIN-Ext*

The results from the EINSTEIN-Ext trial are presented in Table 14. These show that rivaroxaban significantly reduces the rate of recurrent DVTs (HR 0.18 (95% CI, 0.09 to 0.39, p<0.0001). Table 14 shows the constituents (PE and DVT) of the composite outcome (VTE). Both PE and DVT events occur less often in the rivaroxaban arm. The number of clinically relevant non-major bleeding events was increased in the rivaroxaban arm (32 (5.4%)) compared to the placebo arm (7 (1.2%), p<0.001), with a non-significant trend towards an increase in major bleeding events in the rivaroxaban arm, (4 (0.7%)) compared to the placebo arm, (0 (0%), p=0.11). The safety outcome "clinically relevant bleeds" was significantly higher in the rivaroxaban arm, with an HR of 5.19 (95% CI, 2.3 to 11.7, p=0.001), however this outcome is a composite that does not weight the health impact of each event.

[redacted]

Specific adverse events are worse in the rivaroxaban arm (Appendix 2, Table 2), but all cause mortality similar in both arms (Table 13) for both the analyses with DVT and PE patients, and the analyses with the DVT only patients. [redacted]

Table 14: Summary of outcomes for EINSTEIN-Ext, taken from Tables 18 and 29, data on page 59 of MS[1] and data from the Manufacturer's clarification document.[17]

Trial name	**Einstein-Ext**			**Einstein-Ext; DVT patients only**		
References	Bauersachs et al 2010[21] Manufacturer's submission[40]			Manufacturer's clarifications[17]		
Group	**Rivaroxaban N, (%)**	**Placebo N, (%)**	**Hazard ratio (95% CI, p value)**	**Rivaroxaban N, (%)**	**Placebo N, (%)**	**Hazard ratio (95% CI, p value)**
ITT population: Safety population: PP population:	602 598 550	594 590 554	NA	[redacted]	[redacted]	[redacted]
Primary outcome: VTE recurrence ITT population: PP population:	 8 (1.3) NR	 42 (7.1) NR	 0.18 (0.09 to 0.39, p<0.0001) [redacted]	 [redacted]	 [redacted]	 [redacted]
Secondary outcome						
Fatal PE	0	1	NR	[redacted]	[redacted]	[redacted]
PE cannot be ruled out	1	0	NR	[redacted]	[redacted]	[redacted]
Nonfatal PE	2	13	NR	[redacted]	[redacted]	[redacted]
Recurrent DVT	5	31	NR	[redacted]	[redacted]	[redacted]
Adverse events (safety population)						
Clinically relevant bleeding (major or clinically relevant non-major bleeding)	NA	NA	5.19 (2.3 to 11.7, p=0.001)	[redacted]	[redacted]	[redacted]
Major bleeding	4 (0.7)	0 (0)	p=0.11	[redacted]	[redacted]	[redacted]
Clinically relevant non-major bleeding	32 (5.4)	7 (1.2)	p<0.001	[redacted]	[redacted]	
Vascular events On treatment Off treatment (30 day follow-up)	 3 (0.5) 2 (0.3)	 4 (0.7) 0 (0.0)	 0.74 (0.17 to 3.3, p=0.69)	 [redacted]	 [redacted]	
All cause mortality	1 (0.2)	2 (0.3)	NR	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious, drug related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quality of life/patient satisfaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N, number; CI, confidence interval; ITT, intention to treat; PP, per protocol; PTS, post thrombotic syndrome; AE, adverse event.

Our experts believed that patients are treated on an ongoing basis after a recurrent VTE. Furthermore, the ERG does not agree with the manufacturer's statement that assuming longer treatment duration would lead to greater cost-savings. Whilst this may be true in the current economic model for the subgroups of patients for whom rivaroxaban reduces the number of recurrent VTEs, such as patients treated for six or 12 months for their index DVT event (see Figure 3), rivaroxaban appears to be associated with more VTE recurrences in patients treated for three months (compared with patients treated with dual therapy LMWH/VKA for 3 months) and therefore higher costs are likely to be accrued in the rivaroxaban arm. Of note, if bleedings were included, this might not be the case anymore.

The ERG also has concerns about the assumptions made by the manufacturer that patients with a recurrent VTE can only receive dual therapy LMWH/VKA. Indeed, according to the indication in its license,[19,20] rivaroxaban can also be used for the treatment of recurrent VTE. In the current economic model, the use of rivaroxaban will reduce the cost for patients experiencing a recurrent VTE (as this is cheaper than dual therapy LMWH/VKA assuming the monitoring used in the manufacturer's economic model).

Due to the constraints imposed by the current model structure, it was not possible for the ERG to adapt the economic model to assume longer treatment durations and estimate the impact of this on the ICER.

An exploratory analysis was however conducted by the ERG assuming a less intensive monitoring in patients treated with a VKA, therefore reducing the treatment costs of LMWH/VKA for the treatment of the index event and for patients experiencing a recurrence. We did not change the efficacy for patients treated for a recurrence. Results of this analysis are presented in section 6 of the ERG report.

5.2.1.7 Effectiveness data

- *Probabilities of bleeding events and recurrent VTEs whilst on treatment*

The probabilities of recurrent VTEs, CRNM bleeds and major bleeds for patients treated with dual therapy LMWH/VKA were taken directly from the EINSTEIN-DVT trial[50] and are presented in Table 24 with the values used in sensitivity analysis and the PSA. The probabilities were assessed for three time periods; 0-3 months, 3 – 6 months and 6 – 12 months. Note that the values used in the PSA (alpha, beta) are incorrect where no events were observed, and the ERG would recommend an uninformative prior to be used (for example adding 0.5 to both the alpha and beta value).